

Exhibit P

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[Intervention Review]

Single-incision sling operations for urinary incontinence in women

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Editorial group: Cochrane Incontinence Group.

Publication status and date: New, published in Issue 6, 2014.

Review content assessed as up-to-date: 6 February 2013.

Citation: Nambiar A, Cody JD, Jeffery ST. Single-incision sling operations for urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD008709. DOI: 10.1002/14651858.CD008709.pub2.

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ABSTRACT

Background

Urinary incontinence has been shown to affect up to 50% of women. Studies in the United States have shown that up to 80% of these women have an element of stress urinary incontinence. Colposuspension and now mid-urethral slings have been shown to be effective in treating patients with stress incontinence. However, associated adverse events include bladder and bowel injury, groin pain and haematoma formation. This has led to the development of third-generation single-incision slings, also referred to as mini-slings.

It should be noted that TVT-Secur (Gynecare, Bridgewater, NJ, USA) is one type of single-incision sling; it has been withdrawn from the market because of poor results. However, it is one of the most widely studied single-incision slings and was used in several of the trials included in this review. Despite its withdrawal from clinical use, it was decided that data pertaining to this sling should be included in the first iteration of this review, so that level 1a data are available in the literature to confirm its lack of efficacy.

Objectives

To assess the effectiveness of mini-sling procedures in women with urodynamic clinical stress or mixed urinary incontinence in terms of improved continence status, quality of life or adverse events.

Search methods

We searched the Cochrane Incontinence Group Specialised Trials Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and MEDLINE in process; we handsearched journals and conference proceedings (searched 6 February 2013) and searched ClinicalTrials.gov (searched 20 September 2012), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched 20 September 2012) and the reference lists of relevant articles.

Selection criteria

Randomised or quasi-randomised controlled trials in women with urodynamic stress incontinence, symptoms of stress incontinence or stress-predominant mixed urinary incontinence, in which at least one trial arm involves one of the new single-incision slings. The definition of a single-incision sling is “a sling that does not involve either a retropubic or transobturator passage of the tape or trocar and involves only a single vaginal incision (i.e. no exit wounds in the groin or lower abdomen).”

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Data collection and analysis

Three review authors assessed the methodological quality of potentially eligible trials and independently extracted data from the individual trials.

Main results

We identified 31 trials involving 3290 women. Some methodological flaws were observed in some trials; a summary of these is given in the 'Risk of bias in included studies' section.

No studies compared single-incision slings versus no treatment, conservative treatment, colposuspension, laparoscopic procedures or traditional sub-urethral slings. Also no data on the comparison of single-incision slings versus retropubic mid-urethral slings (top-down approach) were available, but the review authors believe this did not affect the overall comparison versus retropubic mid-urethral slings.

The types of single-incision slings included in this review were TVT-Secur (Gynecare), MiniArc (American Medical Systems, Minnetonka, MN, USA), Ajast (C.R. Bard, Inc., Covington, GA, USA), Needleless (Maymana Healthcare, Lisse, The Netherlands), Ophira (Promedon, Cordoba, Argentina), Tissue Fixation System (TFS PTY Ltd, Sydney, Australia) and CureMesh (D.Med. Co., Inc., Seoul, Korea).

Women were more likely to remain incontinent after surgery with single-incision slings than with retropubic slings such as tension-free vaginal tape (TVTTM) (121/292, 41% vs 72/281, 26%; risk ratio (RR) 2.08, 95% confidence interval (CI) 1.04 to 4.14). Duration of the operation was slightly shorter for single-incision slings but with higher risk of de novo urgency (RR 2.39, 95% CI 1.25 to 4.56). Four of five studies in the comparison included TVT-Secur as the single-incision sling.

Single-incision slings resulted in higher incontinence rates compared with inside-out transobturator slings (30% vs 11%; RR 2.55, 95% CI 1.93 to 3.36). The adverse event profile was significantly worse, specifically consisting of higher risks of vaginal mesh exposure (RR 3.75, 95% CI 1.42 to 9.86), bladder/urethral erosion (RR 17.79, 95% CI 1.06 to 298.88) and operative blood loss (mean difference 18.79, 95% CI 3.70 to 33.88). Postoperative pain was less common with single-incision slings (RR 0.29, 95% CI 0.20 to 0.43), and rates of long-term pain or discomfort were marginally lower, but the clinical significance of these differences is questionable. Most of these findings were derived from the trials involving TVT-Secur: Excluding the other trials showed that high risk of incontinence was principally associated with use of this device (RR 2.65, 95% CI 1.98 to 3.54). It has been withdrawn from clinical use.

Evidence was insufficient to reveal a difference in incontinence rates with other single-incision slings compared with inside-out or outside-in transobturator slings. Duration of the operation was marginally shorter for single-incision slings compared with transobturator slings, but only by approximately two minutes and with significant heterogeneity in the comparison. Risks of postoperative and long-term groin/thigh pain were slightly lower with single-incision slings, but overall evidence was insufficient to suggest a significant difference in the adverse event profile for single-incision slings compared with transobturator slings. Evidence was also insufficient to permit a meaningful sensitivity analysis of the other single-incision slings compared with transobturator slings, as all confidence intervals were wide. The only significant differences were observed in rates of postoperative and long-term pain, and in duration of the operation, which marginally favoured single-incision slings.

Overall results show that TVT-Secur is considerably inferior to retropubic and inside-out transobturator slings, but additional evidence is required to allow any reasonable comparison of other single-incision slings versus transobturator slings.

When one single-incision sling was compared with another, evidence was insufficient to suggest a significant difference between any of the slings in any of the comparisons made.

Authors' conclusions

TVT-Secur is inferior to standard mid-urethral slings for the treatment of women with stress incontinence and has already been withdrawn from clinical use. Not enough evidence has been found on other single-incision slings compared with retropubic or transobturator slings to allow reliable comparisons. Additional adequately powered and high-quality trials with longer-term follow-up are required. Trials should clearly describe the fixation mechanism of these single-incision slings: It is apparent that, although clubbed together as a single group, a significant difference in fixation mechanisms may influence outcomes.

PLAIN LANGUAGE SUMMARY

Single-incision sling operations for urinary incontinence in women

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Stress urinary incontinence (leakage of urine on effort or exertion, or on coughing, sneezing or laughing) is a common condition that affects up to one in three women worldwide. It is usually the result of weakening of the muscular support of the pipe that conducts urine (urethra), or weakening of the sphincter (circular) muscle at the base of the bladder, which maintains continence. It is more common in women who have had children by vaginal delivery and in those who have weakness in the pelvic floor muscles for other reasons.

Historically many types of surgery have been performed to treat women with stress urinary incontinence. Over the past 10 years, the accepted standard technique has been the mid-urethral sling operation, whereby an artificial tape or mesh is placed directly beneath the urethra and is anchored to the tissues in adjacent parts of the groin or just above the pubic bone. Examples of such slings that are commonly used are tension-free vaginal tape (TVTTM) and transobturator tape (TOT). These operations are usually quite successful, with success rates approaching 80% or 90%. However, they have been shown to result in significant side effects, which can be bothersome and sometimes even dangerous, such as damage to the bladder caused by tape insertion, erosion of the tape into the urethra during the healing period or chronic thigh/groin pain.

In an effort to maintain efficacy while eliminating some of the side effects, a new generation of slings has been developed, called 'single-incision slings' or 'mini-slings'; these slings are the subject of this review. They are designed to be shorter (in length) than standard mid-urethral slings and do not penetrate the tissues as deeply as standard slings. It was therefore thought that they would cause fewer side effects while being no less effective. Examples of single-incision slings include TVT-Secur, MiniArc, Ajust and Needleless slings, among others.

We looked for all trials that allocated participants at random to single-incision slings versus any other treatment for stress incontinence in women, especially comparisons with mid-urethral slings. We identified a total of 31 trials, involving 3290 women, all of which compared a type of single-incision sling versus a type of mid-urethral sling, or different types of single-incision slings against each other. Overall the quality of the trials was moderate.

We found that subtle differences in the way individual mini-slings work have sometimes made comparisons difficult. TVT-Secur is a specific type of mini-sling that has consistently been shown to provide poorer control of incontinence, along with higher rates of side effects, compared with standard mid-urethral slings. It has already been withdrawn from clinical use.

As most trials currently available for inclusion in this review assess TVT-Secur, trials comparing other single-incision slings versus standard mid-urethral slings were too few to allow meaningful comparisons. Some evidence suggests that single-incision slings were quicker to perform and may cause less postoperative pain, but more trials are needed to adequately assess whether the other types of mini-slings are in fact as good as or safer than standard mid-urethral slings.